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Publicada

Con informe de búsqueda internacional.

(54) Title: INTERMEDIATE FOR THE SYNTHESIS OF AMLODIPINE, PREPARATION PROCESS AND CORRESPONDING UTILIZATION

(54) Título: INTERMEDIO PARA LA SINTESIS DE AMLODIPINO, PROCEDIMIENTO PARA SU OBTENCION Y ÚTILIZACION CORRESPONDIENTE

(57) Abstract

Intermediate product for the synthesis of amlodipine, process for its preparation and its utilization. The intermediate product is 3-amino-4-(2-phtalimide)ethoxy)crotonate of ethyl and has the formula (III). The preparation process comprises the reaction of acetoacetate having the formula (A) with ammonium acetate; it is used for the preparation of the compound having the formula (B) through the reaction of 3-amino-4-[2-(phtalimido)ethoxy]crotonate of ethyl with a derivative of benzylidene.

(57) Resumen

Intermedio para la síntesis del amlodipino, procedimiento para su obtención y utilización correspondiente. El intermedio es el 3-amino-4-(2-ftalimido)etoxi)crotonato de etilo y es de fórmula (III). El procedimiento para su obtención comprende la reacción del acetoacetato de fórmula (A), con acetato amónico; y su utilización es para la preparación del compuesto de fórmula (B) ilevándose a cabo

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## INTERMEDIO PARA LA SINTESIS DE AMLODIPINO, PROCEDIMIENTO PARA SU OBTENCIÓN Y UTILIZACIÓN CORRESPONDIENTE

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#### DESCRIPCION

La presente invención se refiere a un intermedio para la síntesis del amlodipino, a un procedimiento para su obtención y a una utilización del intermedio.

La invención pertenece al campo de la química heterocíclica y, tal como ya se ha indicado, se refiere a un intermedio químico, el 3-amino-4-(2-ftalimido)etoxi)crotonato de etilo, su proceso de preparación, y su utilización para la síntesis del compuesto 2-((2-aminoetoxi)metil)-4-(2-clorofenil)-3-etoxicarbonil-5-metoxicarbonil-6-metil-1,4-dihidropiridina, denominado genéricamente amlodipino, producto con actividad terapéutica utilizado como agente antiisquémico y antihipertensivo.

En la patente EP 0 089 167 se describe la utilización de 1,4-dihidropiridinas de fórmula I, como precursores inmediatos del Amlodipino de fórmula II.

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La patente EP 0 060 674 describe dos procedimientos para la preparación de 1,4-dihidropiridinas que contienen en la posición 2 un substituyente con un grupo amino y que poseen utilidad antiisquémica y

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antihipertensiva, En los dos casos, los rendimientos que indican son muy bajos (≈15%) y los productos tienen que ser purificados por cromatografía, lo que hace difícil su aplicación industrial.

La patente EP 0 089 167 describe la preparación de varias 1,4-dihidropiridinas de fórmula I, precursoras del amlodipino, siguiendo los mismos procedimientos indicados en la patente EP 60674:

(a) En el caso en que los grupos aminoprotectores son bencilo, azido o ftalimido, por reacción del 2-clorobenzaldehido (IV) con el acetoacetato de etilo (V) y 3-aminocrotonato de metilo (VI)

(b) Alternativamente, en el caso en que los grupos aminoprotectores son bencilo y azido, por reacción del benciliden derivado (VII) con el aminocrotonato (VIII), este último preparado "in situ" a partir del acetoacetato de etilo correspondiente (V) y acetato amónico.

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 $NR^1R^2 = N_1$ 

Con ambos procedimientos los rendimientos obtenidos son muy bajos (30% y 11% respectivamente en el caso del grupo protector azido, NR¹R²=N₃). Por otra parte, los aminocrotonatos intermedios (VIII) no se aíslan ni se caracterizan ya que se preparan "in situ" a partir del acetoacetato de etilo correspondiente (V) previamente a la reacción con el bencilidén derivado (VII). En la literatura no se ha encontrado descrito el aislamiento ni la caracterización de estos aminocrotonatos (VIII). Los autores de la presente invención han intentado aislar sin éxito el compuesto de fórmula VIII descrito en la patente EP 0 089 167, siendo R¹ = R² = Bn. Esta patente describe estos compuestos como preparados "in situ" (pág 8), sin ninguna comprobación experimental sobre sus características o estructura química.

Debido a que los acetoacetatos (V) y el benciliden derivado (VII) son aceites, era fundamental disponer de un intermedio sólido que permitiera obtener compuestos de fórmula (I) con alto rendimiento y pureza.

La presente invención se refiere a un nuevo compuesto, el 3-amino-4-(2-ftalimido)etoxi)crotonato de etilo, de fórmula III

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4.

El nuevo compuesto de fórmula III ha podido aislarse en estado sólido permitiendo así su purificación, identificación y caracterización. Este compuesto ha resultado ser muy útil como intermedio para la síntesis de la 4-(2-clorofenil)-3-etoxicarbonil-5-metoxicarbonil-6-metil-2-(2-ftalimidoetoxi)metil-1,4-dihidropiridina (de fórmula I, donde NR¹R² = ftalimido) precursor inmediato del amlodipino.

El procedimiento de preparación de III consiste en la reacción del 4-[2-(ftalimido)etoxi]acetoacetato de etilo (V, NR¹R² = ftalimido) con acetato amónico en un medio de reacción, que preferentemente es un disolvente orgánico (etanol, isopropanol, tolueno, xileno, etc.) rindiendo el producto deseado en estado sólido y con un buen rendimiento y un alto grado de pureza. La reacción tiene lugar a una temperatura entre 10°C y la temperatura de reflujo, preferiblemente entre 50 y 70°C, y con un dispositivo Dean-Stark que permita la separación del agua formada en la reacción. Al término de la misma el producto se cristaliza en un alcohol aislándose en forma sólida, quedando las impurezas disueltas en las aguas madres.

COOEt

NR'R2

$$H_2N$$

(V)

 $NR'R^2 = N$ 

(III)

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Una utilización de interés del 3-amino-4-(2-ftalimido)etoxi)crotonato de etilo (de fórmula III) sólido se obtiene haciéndolo reaccionar con 2-(2-cloro-benciliden)acetoacetato de metilo (de fórmula VII) en un disolvente orgánico (metanol, etanol, isopropanol, tolueno, xileno), preferiblemente etanol, a una temperatura comprendida entre 10°C y la temperatura de reflujo, preferiblemente entre 60 y 80°C. La reacción se mantiene entre 12 y 24 horas, al cabo de las cuales se enfría con lo que cristaliza la 4-(3-clorofenil)-3-etoxicarbonil-5-metoxicarbonil-6-metil-2-(2-ftalimidoetoxi)metil-1,4-dihidropiridina (I; NR¹R² = ftalimido) que se aísla con alto grado de pureza y rendimiento, superior a los descritos en la literatura.

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MeOOC

$$H_3C$$
 $H_3C$ 
 $H$ 

A continuación, se describen unos ejemplos que ilustran la invención.

#### **EJEMPLO 1**

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3-amino-4-(2-ftalimido)etoxi)crotonato de etilo (III)

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32 g (100 m.moles) de 4-[2-(ftalimido)etoxi]acetoacetato de etilo en 200 ml de tolueno se hacen reaccionar con 8,1 g (105 m.moles) de acetato amónico a 65°C durante 4 horas eliminando el agua formada en la reacción mediante un Dean-Stark. Se evapora el tolueno hasta sequedad y el residuo de la destilación se cristaliza en isopropanol rindiendo 24,5 g (rdt. 77%) de un sólido beige que corresponde a 3-amino-4-(2-ftalimido)etoxi)crotonato de etilo .

pf: 90-92°C,

IR(KBr): 3335, 3187, 1675, 1619, 1578, 1540, 1401, 1385 cm<sup>-1</sup>

<sup>1</sup>H NMR (300 MHz, DMSO) δ 7,8 (m, 4H, ar), 7,5 (s,1H, NH<sub>2</sub>), 6,7 (s,1H, NH<sub>2</sub>), 4,4 (s,1H, -CH=), 3,9 (m, 4H, -COCH<sub>2</sub>-, =C-CH<sub>2</sub>O-), 3,8 (t, 2H, -OCH<sub>2</sub>-), 3,6 (t, 2H, -CH<sub>2</sub>N), 1,1 (t, 3H, CH<sub>3</sub>)

#### **EJEMPLO 2**

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4-(2-clorofenil)-3-etoxicarbonil-5-metoxicarbonil-6-metil-2-(2-ftalimidoetoxi)metil-1,4-djhidropiridina.

24.0 g (75,4 milimoles) de 3-amino-4-(2-ftalimido)etoxi)crotonato de etilo y 18,9 g (79,2 milimoles) de 2-(2-clorobenciliden)-acetoacetato de metilo en 64 ml de etanol se calientan a reflujo durante 20 horas. Se diluye la mezcla de reacción con 56 ml de etanol y se enfría para cristalizar el producto. Se obtienen 14,2 g (rdt. 70%) de 4-(2-clorofenil)-3-etoxicarbonil-5-metoxicarbonil-6-metil-2-(2-ftalimidoetoxi)metil-1,4-dihidropiridina.

25 Pf: 150-151°C IR (KBr): 3370, 1712, 1489, 1422, 1392, 1287, 1201, 1122, 1102, 1024 cm

### REIVINDICACIONES

1.- Intermedio para la síntesis de amlodipino, dicho Intermedio
 siendo de nombre 3-amino-4-(2-ftalimido)etoxi)crotonato de etilo, de fórmula III

(III)

2.- Procedimiento para la obtención de un intermedio de nombre 3amino-4-(2-ftalimido)etoxi)crotonato de etilo de fórmula III

(III)

caracterizado porque comprende la reacción del acetoacetato de fórmula

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con acetato amónico, obteniendo dicho intermedio, el cual es objeto de aisiamiento en forma sólida por cristalización en el mismo medio de reacción.

- 3.- Procedimiento según la reivindicación 2, caracterizado porque dicho medio de reacción es un disolvente orgánico.
- 4.- Procedimiento según la reivindicación 2, caracterizado porque dicho disolvente orgánico es etanol, isopropanol o tolueno.
- 5.- Procedimiento de utilización del 3-amino-4-(2-ftalimido)etoxi)crotonato de etilo de fórmula III

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(III)

para la preparación del compuesto de fórmula

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caracterizado por comprender la reacción de dicho 3-amino-4-(2-ftalimido)etoxi)crotonato de etilo con un benciliden derivado de fórmula VII

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(VII)

## INTERNATIONAL SEARCH REPORT

International application No. PCT/ ES 99/00333

IPC 6 COTD 209/48, COTD 401/12 // (COTD 401/12, 209:48, 211:99) According to International Patent Classification (FC) or to both national classification and IPC  BEILDS SEARCHED  Minimum documentation searched (classification system followed by classification symbols)  IPC 6  Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  Decumentation searched other than minimum documentation to the extent that such documents are included in the fields searched  Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  Documentation of document, with indication, where appropriate, of the relevant passages  Relevant to claim No.  Category*  Citation of document, with indication, where appropriate, of the relevant passages  Relevant to claim No.  A 68/01266 A (BYK GULDEN LOMBERG), 25 February 1988  (25.02,88)  Page 12, compound III; page 16; claim 5, compound III.  A EP 89167 A (PFIZER) 21 September 1983 (21.09.83)  1-5  Page 8, compound VI; page 37, method b)  A EP 60674 A (PFIZER), 22 September 1982 (22.09.82)  Claim 8, compound V; exemple 31; page 8, method 2.  A EP 116769 A (PFIZER), 29 August 1984 (29.08.84)  Further documents are listed in the continuation of Box C.  Special entergeties of cited documents:  Special entergeties of cited documents:  Considered to include the publishment and set of acateste relation or other special reason (as specified)  Considered to include the settlement of the sett		·			
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Category* Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No.  A W0 88/01266 A (BYK GULDEN LOMBERG), 25 February 1988 (25.02.88) Page 12, compound III; page 16; claim 6, compound III.  A EP 89167 A (PFIZER) 21 September 1983 (21.09.83) 1-5 Page 8, compound VI; page 37, method b)  A EP 60674 A (PFIZER), 22 September 1982 (22.09.82) 1-5 Claim 8, compound V; exemple 31; page 8, method 2.  A EP 116769 A (PFIZER), 29 August 1984 (29.08.84) 5 Page 12, method b); page 80  Further document are listed in the continuation of Box C.  Special categories of cited documents:  A decomment defining the general state of the art which is not considered to be of particular relevance; the claimed invention at the principle or theory underlying the inventi	Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched				
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